Case Report

A Severe Case of Reye's Syndrome with Multiorgan Dysfunction after Epstein-Barr Virus Infection

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Abstract

A 20-month-old male infant with multiorgan dysfunction after Epstein-Barr virus (EBV) infection developed Reye's syndrome. He also suffered from acute liver failure, life-threatening cerebral edema, severe disseminated intravascular coagulation (DIC), and myocardial involvement. EBV infection aggravated the disease progress of Reye's syndrome definitely, leading to death despite full supportive and symptomatic therapy. This case report suggested that pediatricians should pay attention to multiorgan involvement of severe EBV infection.

CASE DISCRIPTION

A 20-month-old male infant was admitted to the Shengjing Hospital because of fever (39.8°C) and lethargy for three days after receiving vaccination Japanese encephalitis vaccine 4 days ago. The patient cried and screamed, with non-projectile vomiting occasionally. At the local hospital before transfer, due to fever occurred on the second day after vaccination, the patient recieved oral antipyretic administration (ibuprofen) and intravenous anti-inflammatory treatment (cephalosporin, unknown specific dose). The blood test for liver function showed that alanine aminotransferase (ALT) increased to 2754 U/L.

Physical examination on admission: the patient was restless, with bilateral chemosis and pharyngeal congestion, no obvious skin and sclera jaundice. The light reflex of pupils was prompt without anisocoria. The heart and lung were normal on auscultation. A swollen liver was palpable 2.5 cm below the right costal margin, pliable and tough.

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The liver function examination revealed remarkable elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were 5598 U/L and 6233 U/L respectively. Other abnormal indexes included the total protein, 44.3 g/L; albumin, 29.9 g/L; total bilirubin, 120.2 μ mol/L; conjugated bilirubin, 95.2 μ mol/L; unconjugated bilirubin, 25.0 μ mol/L. Serum ferritin was 69ng/ml, which was within a normal reference range. The surface antigen and e antigen of Hepatitis B virus were negative, which indicated that deteriorating liver function was not caused by the infection of hepatitis viruses. Abdominal ultrasonography revealed hepatomegaly and fatty liver. Hepatoprotective therapy was given immediately by intravenous administration of compound glycyrrhizin. The blood ammonia and lactic acid increased to 161.8 mmol/L and 9.1 μ mol/L respectively, consequently, intravenous administration of ornithine aspartate was given to decrease blood ammonia.

The blood glucose was as low as 0.56 mmol/L on admission, and returned to normal in 4 hours after infusion of glucose. Cerebrospinal fluid test at the 10th hour after admission showed elevated pressure of over 50 drops per minute, with components of white blood cells 3×10^6 /L, glucose 3.0 mmol/L, protein 0.3 g/L, chloride 118.0 mmol/L. Negative EBV-DNA by polymerase chain reaction (PCR) of cerebrospinal fluid excluded the diagnosis of EBV encephalitis. Consequently, we gave the patient mannitol (60ml rapid dripping intravenously) to relieve endocranial hypertension, and oxiracetam (4g dissolved in 100ml 15% glucose or 0.9% sodium chloride, inject intravenously) for nutritional therapy of brain cells.

The blood routine examination on admission showed white blood cells (WBCs) 5.2×10^9 /L, the percentages of neutrophils and lymphocytes were basically normal, hemoglobin 109×10^9 g/L, and the platelets (PLTs) decreased slightly to 120×10^9 /L. C-reactive protein was normal. The results above suggested virus infection.

At the 10th hour after admission, the Disseminated Intravascular Coagulation (DIC) test revealed that the platelets prominently decreased to 60×10^9 /L compared with that on admission. By platelet transfusions, the final platelets increased to 112×10^9 /L, although it once was as low as a minimum value of 17×10^9 /L. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged by three times compared with normal reference, fibrinogen (FIB) was significantly lowered, fibrinogen/fibrin degradation products (FDPs) and D-dimer (DD) increased prominently. The patient had severe DIC with bleeding of gastro-intestinal tract. We gave treatment with blood coagulation factor, but did not make any improvement for DIC. The liver function was still in the phase of aggressive deterioration. The bone marrow biopsy performed at the 24th hour after admission

showed hyperplasia of megakaryocyte line without hemophagocytes, which ruled out the diagnosis of hemophagocytic lymphohistiocytosis.

Cardiac enzymes test results showed creatine kinase (CK) 419 U/L, creatine kinase-MB (CK-MB) 72.1 U/L, troponin I (TnI) 0.08 µg/L, which indicated myocardial involvement. Consequently, we performed myocardial protection and symptomatic treatments, including creatine phosphate sodium administration intravenously, plasma exchange, correction of electrolyte imbalance and anti-inflammatory.

There was no family history of hereditary or metabolic disease with this patient. However, the patient's blood test results showed abnormalities in content of multiple amino acids, organic acids, and acylcarnitine. The relationship between these abnormalities of metabolite and the patient's disease is not clear and needs further confirmation.

Pathogens detection by chemiluminescent immunoassay (LIAISON, DiaSorin, Italy) showed serum EBV-IgM antibody positive, with high titer of 160 AU/ml (normal reference, 20-40 AU/ml). Real-Time PCR (ABI 7500, Applied Biosystems, USA) examination showed the viral load of EBV DNA in serum was 1.8×10^5 copies/ml. The both positive serum test for EBV-IgM and PCR results for EBV DNA confirmed the diagnosis of acute EBV infection. Infections from other pathogens were excluded by the negative serum results of influenza virus-IgA, parainfluenza virus-IgA, respiratory syncytial virus-IgA, adenovirus-IgA, rubella virus-IgM, herpes simplex virus-IgM, mumps virus-IgM, measles virus-IgM, coxsackie virus-IgM, echo virus-IgM, human cytomegalovirus-IgM and toxoplasma-IgM.

At the 36th hour after admission, the patient appeared clouding of consciousness and anisocoria, then developed dyspnea quickly. Mechanical ventilation and rescue were performed immediately, however, the condition continued to deteriorate and the patient died finally.

DISCUSSION

Reye's syndrome is a rare illness which occurs mainly in children, characterized by encephalopathy and fatty degeneration of the viscera. At present, the etiology of classical Reye's syndrome is unknown, but viral, toxic, drug-related (especially salicylate intake), vaccination and metabolic factors might be associated with Reye's syndrome.¹

The clinical history and auxiliary examinations of the patient indicated the existence of acute non-inflammatory encephalopathy associated with fatty degeneration of the liver, low blood glucose, high blood ammonia, with abnormal results of metabolic screening. There was no other reasonable

explanation for the hepatic and cerebral abnormalities.^{2,3} Moreover, the patient accepted oral antipyretic administration of ibuprofen after the vaccination, which might be a triggering factor. In summary, the patient without family history of congenital metabolic diseases fulfilled the definition criteria of Centers for Disease Control and Prevention (CDC) of USA for Reye's syndrome.⁴

Thirteen common pathogens for a viral syndrome were tested in this case to seek the potential cause of Reye's syndrome, and only EBV was detected positive. So we speculated this patient had an active EBV infection and developed Reye's syndrome after vaccination.

EBV infection in the childhood is usually mild or subclinical, and is the most common cause of an acute, self-limited, infectious mononucleosis (IM).⁵ However, all of the primary EBV infection, reactivation and reinfection can cause aggressive syndromes featured by multiorgan dysfunction, despite the low incidence.⁶⁻⁹

An extremely rare complication of EBV infection is severe thrombocytopenia.¹⁰ The platelets of the present patient decreased further after admission. Severe and stubborn DIC state was not corrected despite active anti-DIC treatment. The child with Reye's syndrome after EBV infection also suffered from acute liver failure, life-threatening cerebral edema, and myocardial involvement. Comparing to the common clinical manifestation of Reye's syndrome, this patient had received full supportive and symptomatic therapy, but still developed cerebral hernia, leading to rapid worsening of conditions and eventual death.

The patient's bone marrow biopsy results showed no abnormal cells, the platelets (PLT) decreased, but no abnormalities in WBC and RBC, which did not match the diagnostic criteria of hemophagocytosis. In this case, because there was no splenomegaly by abdominal ultrasonography, normal serum ferritin level, combined with pathological findings in bone marrow, the diagnosis of hemophagocytic lymphohistiocytosis can be differentiated.^{11,12}

In conclusion, this is a rare case of Reye's syndrome, which had an acute onset and multiorgan dysfunction after EBV infection. It is well known that EBV has evolved many evasive strategies to impair host body responses, which work synergistically or exacerbates the original diseases. EBV infection in this patient aggravated the progress of Reye's syndrome definitely. The patient died 36 hours after admission despite full supportive and symptomatic therapy. Such a case has therefore highlighted that EBV infection in children with Reye's syndrome deserve more attentions from pediatricians.

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